# A robust platform for engineering multi-input and multi-output (MIMO) circuits in mammalian cells

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Synthetic genetic circuits that can integrate multiple input signals and deliver multiple outputs are increasingly important in cell-based therapy and animal model development. However, synthetic biology remains mostly a microbial-centric discipline, and complex genetic circuits remain challenging to engineer, regardless of the host. Here, through the use of site-specific recombinases (SSRs) and their corresponding recombination sites, we have constructed, in mammalian cells, a suite of multi-input and multi-output (MIMO) circuits, such as a six-input AND gate, half adder, half subtractor, 2:4 decoder, full adder, full subtractor. Moreover, we also created a field-programmable read-only memory (FPROM) device that can select between sixteen two-input logic gates based on four inputs. More importantly, we were able to create all of our computation circuits in a single transcription unit —no linkages between different transcription units are required to achieve the desired functionality. This development bypasses one of the most difficult challenges in synthetic circuit design, and allowed all of our circuits to be successfully implemented on first attempt without optimization. In fact, we have created more than 100 functionally distinct 2-Input-2-Output circuits. This platform provides a powerful tool for high-level mammalian cells reprogramming for animal models development. Furthermore, our circuit design platform minimizes the typical “design-build-test” cycle that plagues the progress of most synthetic biology projects, and illustrates a new paradigm in synthetic genetic logic circuit design.